

## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

**PCT****NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

<b>Date of mailing</b> (day/month/year) 23 February 2001 (23.02.01)	<b>To:</b>  Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE  in its capacity as elected Office
<b>International application No.</b> PCT/US00/18841	<b>Applicant's or agent's file reference</b> P1746R1
<b>International filing date</b> (day/month/year) 11 July 2000 (11.07.00)	<b>Priority date</b> (day/month/year) 12 July 1999 (12.07.99)
<b>Applicant</b> CHISHOLM, Vanessa et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

15 January 2001 (15.01.01)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Pascal Piriou  Telephone No.: (41-22) 338.83.38
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## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>P1746R1</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 18841</b>	International filing date ( <i>day/month/year</i> ) <b>11/07/2000</b>	(Earliest) Priority Date ( <i>day/month/year</i> ) <b>12/07/1999</b>
Applicant <b>GENENTECH, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2     **Certain claims were found unsearchable** (See Box I).

3     **Unity of invention is lacking** (see Box II).

4 With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5 With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6 The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

**16**

None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/18841

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7	C12N15/12	C12N15/10	C12N15/62	C12N15/65	C12N15/69
	C12N15/85	C07K14/435	C07K14/71	C07K16/42	C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CAB Data, STRAND, BIOSIS, EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	MENG Y GLORIA ET AL: "Green fluorescent protein as a second selectable marker for selection of high producing clones from transfected CHO cells." GENE (AMSTERDAM), vol. 242, no. 1-2, 25 January 2000 (2000-01-25), pages 201-207, XP002151701 ISSN: 0378-1119 the whole document ---	1-58
A	WO 96 04391 A (GENENTECH INC) 15 February 1996 (1996-02-15) the whole document ---	
A	EP 0 711 835 A (IMMUNO AG) 15 May 1996 (1996-05-15) the whole document ---	
		-/--

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

1 November 2000

15/11/2000

Name and mailing address of the ISA

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Authorized officer

Hornig, H

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/18841

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<ul style="list-style-type: none"> <li>✓ LUCAS BRIAN K ET AL: "High-level production of recombinant proteins in CHO cells using a dicistronic DHFR intron expression vector." NUCLEIC ACIDS RESEARCH, vol. 24, no. 9, 1996, pages 1774-1779, XP002151702 ISSN: 0305-1048 cited in the application the whole document</li> </ul> <p>---</p>	
A	<ul style="list-style-type: none"> <li>BENNETT ROBERT P ET AL: "Fusion of green fluorescent protein with the zeocin-resistance marker allows visual screening and drug selection of transfected eukaryotic cells." BIOTECHNIQUES, vol. 24, no. 3, March 1998 (1998-03), pages 478-482, XP002151703, ISSN: 0736-6205 cited in the application the whole document</li> </ul> <p>---</p>	
A	<ul style="list-style-type: none"> <li>PRIMIG MICHAEL ET AL: "A novel GFPneo vector designed for the isolation and analysis of enhancer elements in transfected mammalian cells." GENE (AMSTERDAM), vol. 215, no. 1, 17 July 1998 (1998-07-17), pages 181-189, XP002151704 ISSN: 0378-1119 cited in the application the whole document</li> </ul> <p>---</p>	
A	<ul style="list-style-type: none"> <li>MOSSER D D ET AL: "Use of a dicistronic expression cassette encoding the green fluorescent protein for the screening and selection of cells expressing inducible gene products." BIOTECHNIQUES, vol. 22, no. 1, 1997, pages 150-152, 154, 156, 158-161, XP002151705, ISSN: 0736-6205 cited in the application the whole document</li> </ul> <p>-----</p>	

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 00/18841

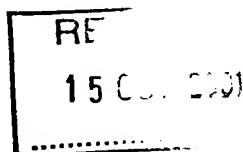
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9604391	A 15-02-1996	US 5561053 A		01-10-1996
		AU 704408 B		22-04-1999
		AU 3204595 A		04-03-1996
		CA 2195303 A		15-02-1996
		EP 0770136 A		02-05-1997
		JP 10503376 T		31-03-1998
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EP 0711835	A 15-05-1996	AT 403167 B		25-11-1997
		AT 209994 A		15-04-1997
		CA 2162770 A		15-05-1996
		US 6114146 A		05-09-2000
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10/019586

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Sean M. WALTON & Others  
Mewburn Ellis  
York House  
23 Kingsway  
LONDON WC2B 6 HP  
GRANDE BRETAGNE



PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year) 11.10.2001

Applicant's or agent's file reference

P1746R1

5903646

## IMPORTANT NOTIFICATION

International application No.  
PCT/US00/18841

International filing date (day/month/year)  
11/07/2000

Priority date (day/month/year)  
12/07/1999

Applicant

GENENTECH, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

## 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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Authorized officer

Hingel, W

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## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1746R1	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/18841	International filing date (day/month/year) 11/07/2000	Priority date (day/month/year) 12/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant GENENTECH, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I     Basis of the report
- II    Priority
- III    Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV    Lack of unity of invention
- V    Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI    Certain documents cited
- VII    Certain defects in the international application
- VIII    Certain observations on the international application

Date of submission of the demand 15/01/2001	Date of completion of this report 11.10.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Giebel, K Telephone No. +49 89 2399 8546



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/18841

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-42                   as originally filed

**Claims, No.:**

1-58                   as originally filed

**Drawings, sheets:**

1/19-19/19           as originally filed

**Sequence listing part of the description, pages:**

1-5, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/18841

the description,      pages:

the claims,      Nos.:

the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):  
*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-58
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-58
Industrial applicability (IA)	Yes:	Claims	1-58
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18841

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The following documents are cited:

D1: GENE, vol. 242, no. 1-2, 25 Jan 2000, pages 201-207  
D2: WO 96 04391 A (GENENTECH INC)  
D3: EP-A-0 711 835 (IMMUNO AG)  
D4: NUCL. AC. RES., vol. 24, no. 9, 1996, pages 1774-1779  
D5: BIOTECHNIQUES, vol. 24, no. 3, March 1998, pages 478-482  
D6: GENE, vol. 215, no. 1, 17 July 1998, pages 181-189  
D7: BIOTECHNIQUES, vol. 22, no. 1, 1997, pages 150-161

2. The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document D1 cited in the international search report could become relevant.
3. INVENTIVE STEP

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claims 1-58 does not involve an inventive step.

- 3.1. The document D3, which appears to represent the closest prior art document, discloses expression plasmids containing a dicistronic transcription-/translation unit comprising a sequence encoding a desired product operably linked to a fusion protein consisting of an amplifiable selectable gene (e.g. the dihydrofolate reductase gene) and a selectable gene (e.g. the hygromycin B phosphotransferase gene).

The polynucleotide according to claim 1 differs therefrom in that it comprises green fluorescent protein (GFP) gene as selectable gene. This difference enables the direct selection of cells containing the nucleotide by fluorescence.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/18841

The technical problem to be solved was thus the provision of polynucleotides which enable a more efficient selection.

The solution as provided by the polynucleotides of claim 1 is considered to lack an inventive step in view of D5. This document discloses expression vectors for the expression of heterologous genes, comprising a fusion of green fluorescent protein (GFP) gene and a Zeocin-resistance gene, and suggests the selection of transfected cells using fluorescence-activated cell sorting (FACS). It would have been obvious to a person skilled in the art to combine the well-known GFP gene with the vector of D3 in order to enable selection by fluorescence. The advantages described in the application would have been reasonably expected by a person skilled in the art. Therefore, claim 1 does not involve an inventive step.

- 3.2. It should be noted that the advantages of GFP in screening and selection were also known from the documents D6 and D7. The document D7 discloses expression vectors in which a gene of interest is operably linked to and under the control of the same promoter as the GFP S65T gene, see Fig. 1 showing the pTR-DC/GFP plasmid which was used to express a c-myc[SPEC0808] sequence. It was also known from the documents D2 or D4 that a desired gene and a selectable gene can advantageously be expressed from a single primary transcript.
- 3.3. Claims 2-58 do also not appear to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, since these features are also well-known from the prior art.

**Re Item VIII**

**Certain observations on the international application**

4. Claims 40 is considered to lack support by the description (Article 6 PCT) since it does not state that the polynucleotide comprises green fluorescent protein gene.